AMENDMENT TO THE SPECIFICATION

Please enter the following amendments to the specification without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents as follows:

Please replace the previously filed Sequence Listing with the replacement Sequence Listing submitted concurrently herewith.

Please delete the paragraphs on page 7, lines 16-26 and replace them with the following paragraphs:

BRIEF DESCRIPTION OF THE FIGURES:

Figure 1A. Nucleotide sequence of alzas **(SEQ ID NO: 12)**.

Figure 1B. (i) Amino acid sequence of ALZASp **(SEQ ID NO: 3)**

(ii) Amino acid sequence of ALZASp3 **(SEQ ID NO: 7)**

(iii) Amino acid sequence of ALZASp4 **(SEQ ID NO: 16)**

Figure 1C. Nucleotide sequence of alzas1 cDNA **(SEQ ID NO: 13)**

Figure 1D. Amino acid sequence of ALZASp1 **(SEQ ID NO: 4)**

Figure 1E. Nucleotide sequence of the 5' upstream regulatory region of alzas gene **(SEQ ID NO: 14)**.

Figure 1F. Nucleotide sequence of alzas2 cDNA **(SEQ ID NO: 37)**.

Figure 1G. (i) Amino acid sequence of ALZASp2 **(SEQ ID NO: 36)**

(ii) Amino acid sequence of ALZASp5 **(SEQ ID NO: 5)**

Figure 1H. Nucleotide sequence of the 5' regulatory region of alzas2 gene **(SEQ ID NO: 38)**.

Please delete the paragraphs on page 9, line 7 to page 10, line 19 and replace them with the following paragraphs:

In detail, the invention provides a nucleic acid molecule, substantially free of natural contaminants, that encodes a protein selected from the group consisting of, alzas, alzas1 and alzas2. In particular, the invention provides the above-described nucleic acid molecule wherein the sequence is, SEQ ID NO:1 and SEQ ID NO: **2**[[5]].

SEQ ID:NO:1

5' ATGGATGCAGAATTCCGACATGACTCAGGATA
TGAAGTTCATCATCAAAAATTGGTGTTCTTTGCAGA
AGATGTGGGTTCAAACAAAGGTGCAATCATTGGACT
CATGGTGGGCGGTGTTGTCATAGCGACAGTGATCG
TCATCACCTTGGTGATGCTGAAGAAGAAACAGTAC
ACATCCATTCATCATGGTGTGGTGGAGGTAGGTAA
ACTTGACTGCATGTTTCCAAGTGGGAATTAA 3'

SEQ ID:NO: **2**[[5]]

5' ATGGATGCAGAATTCCGACATGACTCAGGATA
TGAAGTTCATCATCAAAAATTGGTACGTAAAATAA
TTTACCTCTTTCCACTACTGTTTGTCTTGCCAAAT
GACCTATTAACTCTGGTTCATCCTGTGCTAGAAAT
CAAATTAAGGAAAAGATAA 3'

The invention also provides a protein, substantially free of natural contaminants, selected from the group consisting of, ALZASp, ALZASp1, ALZASp2. In particular, the invention provides the above-described protein having a sequence of, SEQ ID NO: **3**[[2]], SEQ ID NO: **4**[[6]], SEQ ID NO: **5**[[15]]. The invention also provides three associated hypothetical proteins having a sequence of SEQ ID NO: **6**[[3]], SEQ ID NO: **7**[[4]] and SEQ ID NO: **8**[[16]].

SEQ ID:NO: **3**[[2]]

M D A E F R H D S G Y E V H H Q K L V F F A E D V G S N K G A I I G L M V G G
V V I A T V I V I T L V M L K K K Q Y T S I H H G V V E V G K L D C M F P S G N

SEQ ID:NO: **4**[[6]]

M D A E F R H D S G Y E V H H Q K L V R K I I Y L F P L L F V L P N D L L T L V
H P V L E I K L R K R

SEQ ID:NO: 5

M V G G V V I A T V I V I T L V M L K K K Q Y T S
I H H G V V E V G K L D C M F P S G N

SEQ ID:NO: **6**[[3]]

M Q N S D M T Q D M K F I I K N W C S L Q K M W V
Q T K V Q S L D S W W A V L S

SEQ ID:NO: **7**[[4]]

M Q N S D M T Q D M K F I I K N W Y V K

SEQ ID:NO: **8**[[16]]

M W V Q T K V Q S L D S W W A V L S

Please delete the paragraphs on page 10, line 32 to page 12, line 9 and replace them with the following paragraphs:

The invention also provides a method of treating Alzheimer's disease, by providing an individual, in need of such treatment, an effective amount of an antibody or anti peptide substance against, ALZASp, ALZASp1, ALZASp2, [hy1]ALZASp, [hy2]ALZASp and [hy]ALZASp2 or of a reagent to block the activation of the promoters PALZ1-PALZ14 and other regulatory elements which program transcription of, alzas, alzas1, and alzas2 mRNA, having the SEQ IDs, SEQ ID NO: **9**[[7]], SEQ ID NO: **10**[[8]]; SEQ ID NO: **11**[[9]], SEQ ID NO: **15**[[10]], SEQ ID NO: **16**[[11]], SEQ ID NO: **17**[[12]], SEQ ID NO: **18**[[13]], SEQ ID NO: **19**[[17]], SEQ ID NO: **20**[[18]], SEQ ID NO: **21**[[19]], SEQ ID NO: **22**[[20]], SEQ ID NO: **23**[[21]] and SEQ ID NO: **24**[[22]].

SEQ ID:NO: **9**[[7]]

5' TTGATAATTAAATGTTATAGCATGGACACTGACA

TTTACATTTTTTACTTATGTTTTTGGTTTTTAAATGAC

TCTGCAT 3'

SEQ ID:NO: **10**[[8]]

5' ATTATTATTTGAATAATGAAATTCATCAGAACAA

TTA 3'

SEQ ID:NO: **11**[[9]]

5' GCAATTTATAGAAAAGGAAGAGTTCGTAGGTTA

TAAATTCTGTTAGTTGCTAAGAAGCATTTTTAAAA 3'

SEQ ID:NO: **15**[[10]]

5' ATGCTCATTTTTAAAGGCTTTTATTATTATTTCT

GAAGTAATGAGTGCACATGGAAAAA 3'

SEQ ID:NO: **16**[[11]]

5' TATTCCAGGAACAAATCCTTGCCAACCTCTCAA

CCAGG 3'

SEQ ID:NO: **17**[[12]]

5' TAGCATGTATTTAAATGCAGCAGAAG 3'

SEQ ID:NO: **18**[[13]]

5' GAAGGTTTAAATATAGGGTATCATTTTTCTTTA

AGAGTCATTTATCAATTTTCTTC 3'

SEQ ID:NO: **19**[[17]]

5' CCAAATAAAGAGCAAGAATAAAGCAACATTTC A 3'

SEQ ID:NO: **20**[[18]]

5' TTATGCTTTAAAAAGCAATACA 3'

SEQ ID:NO: **21**[[19]]

5' TCCTTTCTTTCAGAATGCCTATTCCTGTGCATTA AAAGTGTCCCTCC 3'

SEQ ID:NO: **22**[[20]]

5' TTTAAAGTAAGCATCAAA 3'

SEQ ID:NO: **23**[[21]]

5' CTTTTTATATAACCTCATCCAAATGTCCCCTGC

ATTTAA 3'

SEQ ID:NO: **24**[[22]]

5' GAAAATGAAATTCTTCTAATTGCGTTTATAAA

TTGTAATTA 3'

Please delete the paragraph on page 14, lines 9-13 and replace it with the following paragraph:

(2) next we used the method of Bucher et al., J. Mol. Biol. 212; 563-578 (1990) to identify putative promoter regions associated with the orf within 100-1000 bp 5' upstream of the translation initiation sequence and we identified potential poly-A addition signals (the consensus poly-A addition sequence is AATAAA **(SEQ ID NO: 25)**) within a region of ~1000 bp 3' downstream from the stop translation codon of the potential orf,

Please delete the paragraphs on page 17, lines 3-24 and replace them with the following paragraphs:

The positional relationship of the ALZAS family of proteins to APP encoding nucleotide sequences on chromosome 21 is shown in FIG. 2Ai. The gene alsas comprises two exons separated by a 5.6 kb intron. The nucleotide sequence of the transcription regulatory region of alzas, which lies within intron 15 of the APP gene, is shown in FIG. 1K. Transcription of alzas can be programmed by any of eight promoters, ("PALZ1") +("PALZ2") SEQ ID:NO: **9**[[7]]; ("PALZ3") SEQ ID:NO: **10**[[8]], ("PALZ4") SEQ ID:NO: **11**[[9]], ("PALZ5") SEQ ID:NO: **15**[[10]], ("PALZ6") SEQ ID:NO: **16**[[11]], ("PALZ7") SEQ ID:NO: **17**[[12]] and("PALZ8") SEQ ID:NO: **18**[[23]], located in the regulatory region. PALZ3/4/5/6/7/8 are correlated with cap sites. Heat shock elements, which can modulate activity of all the alzas promoters, overlaps PAL3 (Heat shock proteins are reviewed by Gething, M. J. and Sambrock, J. Nature 355:33-45 (1992); two putative estrogen responsive elements (Savouret et al., Recent Progress in Hormone Res. 45:69-120 1989; Beato M. Cell 56:355-361 1989), lie ahead of and between PALZ 7/8. A potential poly-A addition site is present in the 3' downstream untranslated region of the gene.

The alzas cDNA is shown in FIG. 1G SEQ ID:NO:1. It includes sequences identical to APP exon 16, exon 17 and part of intron 17, and encodes a 79 amino acid protein ALZASp, SEQ ID:NO: **3**[[2]], shown in FIG. 1Hi. The protein includes the complete A.beta. protein sequence, the APP transmembrane helix sequence (which has a constitutive hormone controlled secretory signal between aa 42//43) and a unique c-terminal sequence that is not related to APP amino acid sequences but has significant homology to a domain in a plant chloroplast membrane protein, and to the c-terminal sequence of ApoE4 proteins as determined with the method described by Feng, D. F. et al. J. Mol. Evol. 21:112-125 (1985).

Please delete the paragraph on page 21, line 27 to page 22, line 8 and replace it with the following paragraph:

The alzas1 cDNA, SEQ ID:NO: **2**[[5]], is shown in FIG. 1D. It encodes a 51 amino acid protein "ALZAS1" FIG. 1E, SEQ ID:NO: **4**[[6]]. ALZAS1 is made up from the first 17 amino acids of Aβ and 34 aa encoded by sequence homologous to APP intron 16. The protein contains a monomeric transmembrane helix and has a "leucine zipper"; it has a secretory signal which, if used, would releases the entire non membrane associated c-terminal domain. The c-terminal of ALZAS1 contain a five amino acid sequence which is identical to ApoE proteins heparin binding site and to the core sequence of ApoE LDL receptor binding sequence. This suggests that

ALZAS 1 might compete with ApoE proteins for binding to the LDL receptor and may be an important etiological factor in AD associated vascular diseases. It also provides additional indication that an evolutionary relationship might exist between ApoE proteins and ALZAS proteins.

Please delete the paragraphs on page 23, lines 11-27 and replace them with the following paragraphs:

The invention is also related to the discovery of a gene we call Alzheimer associated 2 ("alzas2"). The organization of the gene in relationship to alzas is shown in FIG. 2C. It is a single exon gene that is formed from an extended version of alzas exon 2. It is transcribed by six promoter elements ("PALZ9") SEQ ID:NO:**19**[[7]], ("PALZ10") SEQ ID:NO: **20**[[8]] ("PALZ11") SEQ ID:NO: **21**[[9]],("PALZ12") SEQ ID:NO: **22**[[20]], ("PALZ13") SEQ ID:NO:**23**[[21]] and ("PALZ14") SEQ ID:NO: **24**[[22]], located in the 5' upstream regulatory region of the gene. The sequence of the latter region is shown in FIG. 1G; it is homologous to sequences in APP intron 16. It harbours two potential heat shock elements, one upstream of PALZ11 and the other upstream of PALZ14, which may influence activity of the promoters.

The nucleotide sequence of alzas2 cDNA, SEQ ID:NO: **37**[[14]], is shown in FIG. 1F. There are two potential orfs in the cDNA; the most probable orf encodes a 44 amino acid protein ALZAS2, SEQ ID:NO: **5**[[15]], FIG. 1G. The aa sequence of ALZAS2 is identical to sequence 36-79 of ALZAS and can mimic all the activity of ALSAS related to a role in the pathology of AD, described above. Another hypotethical protein ("[hyp]ALZAS2p") SEQ ID:NO: **36**[[16]], which can be translated from alzas cDNA is shown in FIG. 1 Gii; protein fingerprinting indicates it may be a neuropeptide with a wide spectrum of physiological activity.

Please delete the paragraph on page 24, line 29 to page 25, line 20 and replace it with the following paragraph:

There is a remote possibility that the region of chromosome 21 where alzas, alsas1 and alzas2 are located may be a duplicate of a small region of chromosome 21. In this case, these genes may not be obligatory effected by mutations in the full length chromosome. However, it is more than likely that the genes are transcribed from within the APP gene, either in certain subsets of cells, or only when the promoters are sporadically activated by toxic intra/inter

cellular factors produced in neuronal cells or toxic substances that enter such cells from the external environment. Other mutations in chromosome 21 which affect the configuration of DNA sequences in APP exons 16 and 17 and have been linked to early onset AD (Mullan, M. and Crawford, F. Trends neurosci. 16:398-403 1993), may occur also in the alzas genes. The Hardy VI and VG mutation, the VF mutation, and the Dutch EQ mutation that occurs in exon 17 (Selkoe, D. J. A Rev. Neurosci. 17:489-517 (1994); Hardy, J. Clin. Geriatr. Med. 10:239-247 1994)), cause a single amino acid change in ALZASp/p1/p2. However, the DM to QL mutation in exon 16 (Cai, X. D. et al. Science 259:514-516 1993) eliminates the normal orf for ALZASp and ALZAS1p which can lead to translation and expression of alternative proteins using other reading frames. Two hypotethical neuropeptides ("[hyp]ALZASp") SEQ ID:NO: **6**[[3]], shown in FIG. 1Bii, and ("[hyp1]ALZASp") SEQ ID:NO: 7[[4]], shown in FIG. 1 Biii, can be translated from alzas cDNA. Amino acid 23-40 in [hyp1ALZASp] is identical to the sequence of [hyp]ALZAS2p. If expressed, the hypotethical proteins might play a role in the etiology of AD, and also lead to variations of the disease phenotype e.g., the mutation at codon #713 that causes schizophrenia, Jones, C.T. et al. Nature Gene. 1:306-309 (1992)), and the mutation at codon #702 that leads to hereditary cerebral haemorrhage, Dutch type (Levy, E. et al. Science:248 1124-1126 (1990)), may cause alterations in the biochemical property of at least one of the hypotethical proteins.

Please delete Table 1 and replace it with the following table:

Table 1A

PCR primers used to detect mRNA in lymphocytes and brain

alzas 287	product size expected =	287 bp
Forward	GTGGACAAATATCAACACCGAGGAC **(SEQ ID NO: 26)**	
Reverse	ACATAGTCTTAATTCCCACTTGG **(SEQ ID NO: 27)**	
alzas 393	product size expected =	393 bp
Forward	GTCCTGCATACTTTAATTATGATG **(SEQ ID NO: 28)**	

Reverse AGCCATCATGGAAGCACACTGATTCG **(SEQ ID NO: 29)**

alzas 188 product size expected = 188 bp

Forward GTGGACAAATATCAAGACGGAGGAG **(SEQ ID NO: 30)**
Reverse TCCTTAATTTGATTTCTAGCACAGG **(SEQ ID NO: 31)**

alzas 267 product size expected = 267 bp

Forward TCCTGCATACCTTTAATTATGATG **(SEQ ID NO: 32)**
Reverse TTCATGGTAATCCTATAGGCAAC **(SEQ ID NO: 33)**

alzas 148 product size expected = 148 bp

Forward GTGTTCTTTGCAGAAGATGTGGG **(SEQ ID NO: 34)**
Reverse ACATAGTCTTAATTCCCACTTGG **(SEQ ID NO: 35)**